Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition while Promoting Human Health

Part II: Drug Disposal, Waste Reduction, and Future Direction

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running title:
Pollution Prevention for Drugs in the Environment — Part II

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acronyms:
EMEA: The European Agency for the Evaluation of Medicinal Products
EPR: Extended Producer Responsibility (now called Product Stewardship)
FDA: U.S. Food and Drug Administration
IOM: Institute of Medicine
LTCF: long-term care facility
PPCPs: pharmaceuticals and personal care products
OTC: over the counter (non-prescription)

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ABSTRACT

Since the 1980s, the occurrence of pharmaceuticals and personal care products (PPCPs) as trace environmental pollutants, originating primarily from consumer use and actions as opposed to manufacturer effluents, continues to become more firmly established. The growing, worldwide importance of freshwater resources underscores the need for ensuring that any aggregate or cumulative impacts on (or from) water supplies be minimized.

Despite a paucity of effects data from long-term, simultaneous exposure at low doses to multiple xenobiotics (particularly non-target-organism exposure to PPCPs), a wide range of proactive actions could be implemented for reducing or minimizing the introduction of PPCPs to the environment. Most of these actions fall under what could be envisioned as a holistic stewardship program — overseen by the healthcare industry and consumers alike. Significantly, such a stewardship program would benefit not just the environment — additional, collateral benefits could automatically accrue, including the lessening of medication expense for the consumer and improving patient health and consumer safety.

This paper (the second of two parts describing the "green pharmacy") focuses on those actions and activities tied more closely to the end user (e.g., the patient) and issues associated with drug disposal/recycling that could prove useful in minimizing the environmental disposition of PPCPs; the first part focuses on the background behind the imperative for an ecologically oriented stewardship program for PPCPs and presents activities and actions for pollution prevention that reside more under the control of the health-care industry (further up the chain of events involved with a drug's cradle-to-grave disposition). This second part also outlines some recommendations and suggestions for further research and poses some considerations with regard to the future.

This two-part document attempts to cohesively capture for the first time the wide spectrum of actions available for minimizing the release of PPCPs to the environment. A major objective is to generate an active dialog or debate across the many disciplines that must become actively involved to design and implement a successful approach to life-cycle stewardship of PPCPs.

SECTION OUTLINE

INTRODUCTION

This paper is the second of a two-part examination (Daughton 2003a,b) of the many facets of a little-discussed, but very important, aspect of the overall issue of PPCPs as environmental pollutants — namely, pollution prevention. In light of the fact that trace residues from this large, diverse galaxy of sometimes highly bioactive chemicals gain entry to the environment simply by way of their usage and disposal (Daughton 2001a, Daughton and Jones-Lepp 2001, Daughton and Ternes 1999, Heberer 2002, Kolpin et al. 2002, Kümmerer 2001, Servos et al. 2002), and regardless of what little is known regarding the consequences for ecological or human health (Daughton 2001a, Daughton and Ternes 1999), a wide spectrum of actions can be taken to minimize or eliminate their further environmental disposition. Significantly, these actions toward pollution prevention (e.g., source reduction/control) hold the potential at the same time for beneficial human health consequences unrelated to their occurrence as pollutants. This second of two parts (Daughton 2003b) focuses on those source control/reduction activities tied more closely to the end user (e.g., the patient and consumer) and issues associated with drug disposal/recycling rather than those that reside more under the control of the health-care industry (further up the chain of events involved with a drug's cradle-to-grave disposition), which is the focus of the first part (Daughton 2003a). This second part also outlines some specific suggestions centering more on end-use, presents recommendations for further research, and poses some considerations with regard to the future; the background and context for why pollution prevention is a topic worth considering for PPCPs is covered in the first part.

With its focus on pollution prevention (e.g., source elimination or minimization) via voluntary actions, as an alternative to conventional pollution control via prescribed standards, this two-part paper is intended as a companion piece to the review (Daughton and Ternes 1999) published in *Environmental Health Perspectives* that focused primarily on the origins and environmental occurrence of PPCPs together with an introduction to what little was known at that time about the potential for adverse ecological effects.

One of the major objectives of this paper is to generate an active dialog or debate across the many disciplines that must become actively involved to design and implement a successful approach to life-cycle stewardship of PPCPs — an approach that not only minimizes their potential to impact the environment, but one that also could collaterally improve medical healthcare outcomes for consumers and reduce healthcare costs. While the onus for environmental stewardship primarily rests with the larger healthcare community (including the consumer), almost no discussion of the overall issue has taken root in the medical literature (Daughton 2002). A cohesive, scientifically sound set of guiding principles could be adopted by the industries involved with manufacturing, packaging, distribution, and purveyance of PPCPs — principles that would also serve to influence or guide consumer actions. By focusing on developing an industry consensus and cultural mind set toward holistic environmental responsibility, rather than relying on compliance to regulations, all sectors of society could play integral, productive roles in striving for a sustainable environmental environment.

DRUG DISPOSAL/RECYCLING/POLLUTION PREVENTION:

Responsible Disposal and Product Stewardship: Of all the inquiries received from the public and the news media on the topic of PPCPs in the environment, the most frequent regards "proper" (ecologically sound) disposal of unused medications. Unfortunately, definitive, consistent guidance is not available. The age-old wisdom of flushing medication down the toilet (still recommended by many professionals), however, is probably the least desirable of all the alternatives, which include disposal in household trash and community hazardous waste pickup programs. Indeed, standardized nationwide or international guidance is needed for disposition of non-controlled substances by end-users of unused/expired drugs as well as by disposal companies. A formal but voluntary Product Stewardship program (previously known as Extended Product Responsibility, EPR; see: Hanisch 2000; U.S. EPA Office of Solid Waste 2002) implemented by all involved industries would be a proactive way to guide the disposal of unwanted, expired ("out-dated") PPCPs by the public, state, local, and medical communities (e.g., nursing homes, hospitals, physician samples). National policies are usually directed solely at the internal generation of wastes by the medical care industry – not by the public. For example, Australia (NHMRC 1999) advises "Wherever possible, this waste should be incinerated. It should not be sent for landfill. Such waste should not be discharged into sewerage systems" (p. 14). Little exists in the peer-reviewed literature regarding drug disposal regulations and attendant issues. Within the gray literature, four of the more informative resources are Musson and Townsend (1998), Smith (2002), Wang (2000), and WHO (1999). The ideas embodied in EPR, incidentally, have evolved separately from those of "industrial ecology" but the principles of closing the loops for material flows is shared by both. The first professional society devoted to industrial ecology was recently formalized (Yale 2001).

Incentives: One of many possible approaches to fostering stewardship programs (those that tie both environmental and human health together – "ecology of health", see Part I, "Health of Ecology Versus Ecology of Health," Daughton 2003a) would be to offer patent extensions to companies that formulate vibrant, comprehensive stewardship programs tailored for each particular drug. Precedent for this resides in what was FDA's "Pediatric Rule" (an incentive-based rule that encouraged clinical trials designed for children; CDER 2002), since replaced by the Best Pharmaceuticals for Children Act (U.S. FDA 2002a), which offers 6-month patent extensions for doing research that defines safe dosages for children. Interestingly and ironically, the rationale for this need is that it is not possible to predict the differing responses from children (compared with adults) – the same as what might very well be true for potential effects on non-target organisms.

Expanded Use and Mission of Reverse Distributors: Many but not all U.S. pharmacies use "reverse distributors" for return of unsold/expired inventory (e.g., see: RIA 2002; RxWebPortal.com 2002). This existing industry could serve as the foundation for an overarching returns industry — by its expansion into a larger, comprehensive disposal/recycling program, one that accommodate the consumer sector. Great value could be added by designing an integral database that compiled information mined from consumer returns, with the objective of ultimately improving health care (see below: "Take-Back Programs"); this type of data is traditionally extremely difficult to obtain.

Pharmaceutical "returns" result directly from the many issues associated with "unsaleables" (products unwanted by the consumer, for any of a wide spectrum of reasons), a topic whose entire scope is not even understood by the involved industries, but one which has been captured in a report by Siecker (2001). The monetary costs associated with returns in the U.S. have been estimated at up to (or even exceeding) $2B per year, exceeding the actual market value of the products (Siecker 2001); these costs, however, have never been factored in to a cradle-to-cradle approach. Clearly, many inefficiencies exist in the distribution system. The many forces that cast a product into the unsaleable class have been enumerated by Siecker (2001); these range from simple expiry issues to new market forces (rapid obsolescence by market-entry of new products) to seasonal demand. Industry has brain stormed on ways to reduce the need for returns (Siecker 2001), and some of the ideas comport with those presented in this two-part paper. That the returns industry is so large and because it is driven by the many vagaries of consumerism perhaps casts some light on the scope and magnitude of the parallel issues with consumer creation of unused drugs. The total cost for drugs that are placed into the returns network amounts to a little more than 1% of total sales. The 2002 *Chain Pharmacy Industry Profile* (NACDS 2002) reports $164B in 2001 total retail pharmacy sales resulting from over 3 billion scripts, representing two-year increases of 13-16% in sales and 5-6% in scripts; for 2002, $188.5B in sales are projected for 2002 (a 15% increase from 2001). Four of every five patients leave the doctor's office with a prescription (NACDS 2002), so the distribution of drugs through the consumer sector is clearly enormous.

Physician Samples: Although physician samples (those manufacturer samples distributed free to medical practices) constitute an unknown percentage of the overall disposal problem, distributors of physician samples often instruct physicians to dispose of out-dated samples to the sewage system. This source should also be subject to any nationwide guidance or regulations.

Source Separation for Domestic Wastes: Advancement in, and implementation of, new technologies for dealing with waste at the source (e.g., separation of distinct streams) holds the highest potential for the future minimization of waste flows to the environment. Sewage source separation schemes, such as those involving toilet re-engineering, are but one example (e.g., Larsen et al. 2001; Novaquatis 2002; Otterpohl 2002).

Sewage Recycling: Also under development are various "toilet-to-tap" plans for upgrading sewage to potable water (or at least to a level suitable for groundwater reinjection) (Drewes and Shore 2001; Greene 2000). By use of advanced water treatment technology such as reverse osmosis (RO), nearly complete removal of all PPCPs can be achieved. It deserves noting, however, that all of the solutes removed by RO are concentrated in the rejected "brine" — a waste stream that must be disposed itself.

Improvements to Sewage Infrastructure (also see: Part I, "Key Importance of Water Resources — Impact of Untreated Sewage," Daughton 2003a): Straight-piping of sewage (e.g., see: Pressley 1999) to surface waters should continue to be identified and eliminated on an ongoing basis. Privies and septic systems should be converted to municipal systems when feasible. Improvements in capacity can reduce overflow events, a problem of escalating proportions in many urban areas (see extensive news series on aging sewer infrastructure: Sforza et al. 2001). It has been long assumed that ocean discharge of sewage protects costal exposure (by way of dilution). Recent study, however, shows the possibility of sewage plume redirection to coastal areas by tidal events (Boehm et al 2002). As sewage discharges increase with expanding populations, what dilution previously afforded by receiving waters will continually diminish.

Recycling (reclamation): "Drug mining," such as hospital reclamation of highly toxic drugs from excreta and other wastes, could be pursued and expanded; as a prototype example, see Tru-Kinase (2002).

Responsible Re-Use, Recycling, Donation: The entire area of charitable drug donations and pharmacy re-use (sometimes referred to as recycling) is a complex issue — one fraught with concerns especially regarding safety, liability, and compensation. Donations are complicated by a morass of international regulations, politics, interconnected organizations and charities, and controversy (Reich 1999). One of the technical issues associated with drug donations and re-use is that of expiry. More information can be found at the web site maintained by the Wemos Foundation (2002). Certain state legislation in the U.S. (for a recent example, see: Ohio General Assembly 2001) has been attempting to establish drug "repository" programs for collecting and redistributing unadulterated prescription drugs for subsequent re-prescribing to patients meeting eligibility requirements.

The re-use by pharmacies of previously prescribed, within-date drugs has been a contentious and complex issue for over two decades – one which has become even more so because of the rising costs of new-generation drugs and because of insufficient public resources dedicated to the medically indigent. There is also debate as to whom should benefit (in terms of compensation) from re-use being that the original patients, insurance companies, or Medicaid programs originally paid for the unused medications.

Dispensing laws often run counter to responsible re-use of still-usable drugs (OSU 2000a), this despite the fact that modern, tamper-evident packaging would greatly assist in the assurance of quality of re-used drugs. In Oklahoma alone, LTCFs (long-term care facilities) each month are directed by state law to dispose of millions of dollars of unused medications (and incur substantial personnel oversight/implementation costs); an unknown portion of the disposed drugs are directed to municipal sewers. At the same time, the medically indigent often do not receive medications that they may require, and when they do, it is often necessary to use public funds (OSU 2000a).

One rough estimate of the national monetary value of unused drugs in LTCFs is $73-378M (OSU 2000a); statistically based estimates are difficult to compile because of the proprietary nature of the industry. This estimate assumed wastage rates of 4-15%, which have been revealed by various state studies (OSU 2000a).

It is illegal in certain states (e.g., Oklahoma) to give away (e.g., donate to charity) any drug already obtained by prescription (OSU 2000a,b). It is also illegal in certain states for pharmacies to accept returned unused drugs; this is a result of long-recognized, complex issues regarding quality assurance (particularly problematic is a drug's shelf history – whether it was stored in a controlled environment, especially with regard to temperature and humidity – as well as the issue of counterfeiting). Because of these complicating factors, the FDA has no general policy governing re-use and instead prefers that each state set its own individual policy (OSU 2000b, Exhibit 10); the FDA does not disallow re-use – it simply highlights the dangers and pitfalls that require vigilance in establishing a re-use program. The AMA supports the re-use of drugs in LTCFs (AMA 2001). In light of this, it behooves the states to study and emulate best practices and try to align their practices accordingly.

Demonstrating the disparate implementation of drug re-use across the U.S., it has proved difficult to ascertain exactly what state practices do entail. One survey maintains that as of the year 2000, there were 36 states allowing at least some form of drug re-use (recycling) or resale; 17 allowed both re-use and resale without restrictions, and 12 prohibited any re-use or resale (OSU 2001, 2000b, Exhibit 12, Table 1). A subsequent survey (OSU 2001), however, revealed only six or so states with re-use/resale provisions. It is clear that the issue is complex, with different meanings, interpretations, and implementation across the states. Certain states have been actively working on legislation that would enable re-use; Ohio (Ohio General Assembly 2001) and Oklahoma (OSU 2001) are two examples.

Environmentally Sound Funeral Practices: In those countries practicing burial, cemeteries (which in reality are a special landfill sub-class; Ucisik and Rushbrook 1998) can pose problems with respect to groundwater pollution if they have not been properly engineered and sited with local hydrogeologic processes in mind (Croukamp 1999). While a number of investigations have examined the transport from burial grounds of pathogens to the groundwater (Santarsiero et al. 2000), little is known with regard to the release of PPCPs, whose presence in dead bodies could be expected to be extensive as a result of long-term medication and heroic treatment measures. Furthermore, in North America, those areas where embalming is practiced commonly discharge withdrawn body fluids (containing whatever medications the dying patient had been administered) directly into municipal sewage systems (Funeral Consumers Alliance 2002). An analogous problem might exist with the disposal of carcasses from medicated or euthanized pets (see Daughton 2001a), where lethal concentrations of barbiturates such as sodium pentobarbital are often used.

Public Outreach/Education – Heightening Public Awareness: A well-designed, concerted public outreach program for communicating the issues associated with PPCPs as environmental pollutants could accomplish dual aims: (1) enhance the public's appreciation and understanding of a wide range of principles associated with environmental science, and (2) increase the public's sense of environmental responsibility by showing (i) how their actions as individuals collectively contribute to the burden of PPCPs in the environment, (ii) how PPCPs can possibly affect environmental processes (e.g., aquatic biota), and (iii) the collateral advantages (human health and economic) accrued by conscientious/responsible disposal and usage of PPCPs. The educational aspects of the topic are summarized by Daughton/EPA (Web page 2002a).

Two additional potential opportunities exist with leveraging the public education aspect of PPCPs as environmental pollutants: (1) The fact that drugs can theoretically be monitored in sewage now provides society for the first time ever with the science-based wherewithal to quantify the actual extent and magnitude of community-wide usage of illicit/abused drugs (see proposal set forth in Daughton 2001b); this would serve to objectify the decades-old and emotionally charged national debate regarding the actual magnitude of drug abuse. (2) Parallel to this is that monitoring for illicit drugs in sewage or the environment could raise community awareness of inadvertent financial support to terrorism (see: Daughton/EPA 2001a; ONDCP 2002). These activities, in turn, would heighten the public's awareness of the fact that their combined, daily individual activities, actions, and behaviors can have immediate, intimate, and inseparable connections with the environment and with world events. With improved knowledge of these connections, behaviors (e.g., consumerism) impacting pollution prevention, disposal, and recycling may eventually become self-adjusting or self-regulating.

DRUG ALTERNATIVES: A variety of approaches, ranging from nutritional to advanced use of medical microbial ecology, could be capitalized on to reduce society's use of medications.

Nutrition and Health Maintenance: The key and critical disease-prevention role played by nutrition should continue to be explored and emphasized at all levels. A number of federal agencies and organizations are active in purveying information regarding the critical linkage between nutrition and health (wellness or disease prevention), including the CDC (2002a), Health Canada (2002), and USDA (2002a,b). This type of information could be made an integral, visible part of DTC advertising for drugs (see Part I, "Advertising," Daughton 2003a). The connections between health maintenance/improvement via proper nutrition and the reduced need for medication are well documented.

Placebos: While "alternative" medicine (e.g., standardized, bioactive, naturally occurring substances such as phytochemicals and other "nutraceuticals") has received much renewed attention (see discussion in Daughton and Ternes 1999), and could eventually serve to reduce the use of synthetic drugs, more emphasis could be placed on expanding the exploration of non-chemical alternatives to traditional medications. As an example, more research could be directed at reducing (or eliminating) drug dosages via the use of placebos (e.g., see refs at: Christensen 2001; also see: Leuchter et al. 2002).

Probiotics: Probiotics (beneficial, endogenous microflora) have long been used and studied for the protection of the gut (largely by blocking pathogen adhesion; e.g., Kaur et al. 2002). More recent work has expanded this important domain of clinical microbial ecology to other medical uses such as prophylaxis for post-surgical infection (in lieu of prophylactic antibiotics; e.g., see: Harder 2002; Reid et al. 2001). The U.S. FDA Center for Veterinary Medicine (CVM) approved the first probiotic for animals (known as a "competitive exclusion culture" product) in 1998; still the only approved competitive exclusion product, it is known by the trade name PREEMPT, and its NADA (new animal drug applications) number is 141-101 (U.S. FDA 2002b). Sometimes called "bacteriotherapy," the wide range of medical uses of probiotics for displacing pathogens is summarized by Beale (2002).

RESEARCH & DEVELOPMENT: Further research and development on a wide range of fronts could contribute to the minimization of PPCPs in the environment. Several are summarized here.

Determining the relative importance of sources:

Disposal vs. Excretion/Washing: Determine the relative contributions to environmental loadings of PPCPs from direct, purposeful disposal to sewage (and trash) of unwanted/unused PPCPs versus inadvertent excretion and washing. That portion of the overall environmental drug burden emanating from direct disposal versus end use is totally unknown. More extensive public surveys and actual monitoring could be used to tease these apart. For example, it might be reasonably surmised that for those oral drugs that (1) are efficiently absorbed and undergo extensive, nearly complete metabolism and low excretion of the parent form (several of many examples include imipramine, morphine, itraconazole, isoproterenol, meperidine, verapamil) and (2) also are documented to occur in the environment, perhaps it could be concluded that direct disposal is probably playing a significant role in their entering the environment. Bathing would be expected to be the most significant source for those drugs that are extensively applied externally (e.g., silver sulfadiazine burn cream) and other topically applied antibiotics (e.g., bacitracin) as well as for personal care products (e.g., synthetic musk fragrances) but disposal could play a role.

Disposal from LTCF vs. General Population: The accumulation of unused medications at long-term care facilities (LTCFs) presents major, well-documented problems for disposal. It is not known, however, how significant this source is compared with disposal from the general populace. This issue grows more important as our population's age-structure becomes more inverted.

Maintenance vs. Short Term: The relative overall contributions to the environment by long-term maintenance drugs (used extensively at LTCFs) versus short-term drugs is not known.

Hospitals vs. Domestic: The use of on-site waste reclamation and treatment varies greatly for hospitals and other medical care facilities. Hospitals might especially be expected to be more significant contributors for certain highly toxic drugs such as antineoplastics and other cytotoxic drugs.

Domestic Animals vs. Humans: Determine the relative contributions from veterinary animals (e.g., confined animal feeding operations [CAFOs], aquaculture, pets) versus humans. This is especially important with regard to steroids (e.g., Renner 2002) and antibiotics (certain antibiotics and anabolic steroids are used exclusively for various domestic animals), where the overall loadings could be important. While the discussion in this paper has focused on human therapeutics, veterinary drugs clearly have the potential to be major contributors to environmental exposure (e.g., see Boxall et al. 2002).

Straight-piping and Raw Sewage vs. Treated Sewage: Straight-piping side-steps what benefits that might exist in secondary and tertiary sewage treatment for further drug removal, so the relative contributions from straight-piping versus treated sewage would be useful to know. Over-flow discharge of raw, untreated sewage is becoming more prevalent as aging and under-capacity treatment plants cannot keep pace with urban populations. Waivers for over-capacity over-flows are frequently granted for discharges to marine environments, in contrast to straight-piping and malfunctioning septic systems, which can be found discharging into any type of receiving water. Another potential source of PPCPs from raw sewage (although more geographically confined) is cruise ships, which have a history of discharge of insufficiently treated sewage (Alaska Department of Environmental Conservation. 2001a,b, 2002; Nowlan and Kwan 2001).

Illicit vs. Licit Drugs: The prevalence of illicit drugs in the environment is completely unknown (Daughton 2001b). While the occurrence database for licit drugs continues to be expanded, with new publications appearing frequently, almost no effort has been devoted to illicit drugs.

Effect of Health Status on Excretion: Health or disease status probably has a large but undetermined significance with respect to determining the extent of excretion of drugs in their unaltered states. Gastrointestinal disease can dramatically reduce uptake and thereby enhance excretion (or expulsion, e.g., through vomiting) of the parent drug. Sequestration (e.g., chelation of tetracycline by dairy products or of fluoroquinolones by divalent cations), alteration in gastrointestinal mobility, or alteration of gastric pH can similarly alter excretion. A better understanding of these parameters for the individual patient would not only better serve patients (e.g., by altered delivery routes), but could reduce unnecessary excretion.

Release into Waters with Low vs. High Existing Pollutant Loads: An argument can be made that windows of aquatic toxicity vulnerability open as a dynamic function of the rate of change or status of overall cellular stress. Organisms that have accommodated to new stress (for example by synthesis of cellular stress proteins or over-expression of efflux pumps) may be significantly more resistant to the effects of newly present toxicants than those organisms equilibrated to a constant environment. For this reason, organisms in slowly changing, pristine environments may be more susceptible to NEW exposure to chemical stressors than are organisms experiencing on-going exposure to many, changing stressors.

New Drugs and Ecotox: Regardless of the environmental significance of the current universe of drugs, the anticipated continuing expansion in new drug entities (those from new chemical classes and with previously unknown mechanisms of action – whose development will be driven largely by advancements on the many fronts of "omics") provides the opportunity to develop ecological toxicity testing approaches that are more capable of detecting the types of effects that could ensue. Particular attention should be paid to accounting for shared mechanisms of action (to accommodate cumulative exposure; see Part I, Fig. 2, Daughton 2003a). Also needed is attention to chemicals that are not necessarily toxic in their own right but which can potentiate the toxicity of other substances ("chemosensitizers"). A good example of this concern is the possible need to screen for a pollutant's potential to inhibit multi-drug efflux pumps, which serve as the first lines of defense for aquatic organisms (Daughton and Ternes 1999; Daughton 2001a; Epel and Smital 2001); this would obviously be important for the new generations of efflux pump inhibitors themselves, but would apply to any PPCP having efflux-pump inhibition potential. As just one example of a new therapeutic class of drugs that may pose environmental concern, consider the angiogenesis inhibitors (see overview at Hourani 2002). This broad therapeutic class comprises a number of synthetics – including legacy drugs, such as thalidomide, as well as many new ones. These compounds have profound teratogenic potential (thalidomide being a well-known example), but little is known with respect to aquatic toxicology (especially important during embryogenesis and development).

Early Warning Monitoring: A nationwide, universal early-warning water monitoring system capable of detecting any newly appearing xenobiotic (including PPCPs) would be tremendously useful for detecting new trends (including illicit drugs) and for permitting early intervention as needed, before adverse impacts might occur. A proposal on the utility of an early-warning monitoring system based solely on the simple approach of identifying anomalous constituents exclusively (largely ignoring all pre-existing constituents) has been outlined (Daughton/EPA 2001b). A collateral benefit from a real-time early-warning monitoring system is that it could be easily designed to serve double duty for homeland security – to detect any newly present chemical sabotage agent. A monitoring system is also a key component of any effort to measure the effectiveness of pollution prevention strategies that have been implemented (in keeping with EPA's new Innovation Strategy: Gibson 2002; U.S. EPA 2002). In recent years, there have been a number of proposals for creation of a national health monitoring system – one based on epidemiology and environmental monitoring, illustrated recently by a meeting sponsored by the Institute of Medicine's Roundtable on Environmental Health Sciences, Research, and Medicine (IOM 2002). A nationwide early-warning monitoring system for previously unrecognized or newly emerging pollutants could be integrated within such a system. Furthermore, the system could be expanded to include the tracking of environmental health in addition to human health pollutants – since the argument can be made that the two are inseparable (see Part I, "Health of Ecology Versus Ecology of Health," Daughton 2003a).

Guidance on Groundwater Recharge: With dwindling supplies of potable water supplies in many parts of the world, efforts to recycle water are accelerating (Drewes and Shore 2001). One approach is to store treated sewage in aquifers by a variety of active re-injection or recharge approaches. While this approach seems straightforward, the fact that the environmental half-lives of many substances are increased in the subsurface domain (because of reduced microbial activity, lack of photolytic alterations), it is imperative that reinjected water is cleaned to standards protective of ecological and human health. Consistent, national guidance (but which can be tailored to local geology) is therefore needed regarding the composition of active recharge waters.

Extended Expiry: Extend the shelf-life research already being performed for factory-sealed drugs under the SLEP (see Part I, "Science-Based Expiry Dates", Daughton 2003a) to see if expiration dates on public-sector factory-sealed drugs and pharmacy-dispensed drugs can be extended or maximized.

Excipients and "Alternative" Medicines: Even though registered drugs and diagnostics have a paucity of data regarding potential or actual environmental effects (other than for conventional ecotoxicological tests), excipients (the non-therapeutic agents in formulated medicines), alternative drugs such as nutraceuticals and dietary supplements, and personal care products (with the exception of the synthetic musk fragrances, some surfactants, and sunscreen agents) have even less. Some research effort should be devoted to these under-investigated classes of PPCPs in the environment to gage their possible importance. The diverse classes of bioactive chemicals in nutraceuticals and dietary supplements is growing as a result of renewed interest in "self-care." Several examples are summarized in Daughton and Ternes (1999). In contrast to the usage of pharmaceuticals (with the exception of "cosmetic" or "lifestyle" pharmaceuticals), consumer use of personal care products is almost always one of personal discretion. Also unlike pharmaceuticals, most personal care products are used externally (or not ingested) and in larger quantities, maximizing their likelihood for release to the environment (via bathing or oral discharge).

FUTURE CONCERNS/OPPORTUNITIES

Molecular Farming ("Pharming"): The large-scale production (kg/ha) of pharmaceuticals by means of transgenic organisms, especially plants and food crops (known as molecular farming or "pharming"), is currently aimed mainly at producing phytopharmaceuticals — "functional foods," "biologic," and other medically related reagents, diagnostics, and vaccines. Today, molecularly farmed pharmaceuticals are primarily recombinant proteinaceous therapeutics, such as enzymes, hormones, and monoclonal antibodies, that tend to be costly to produce by existing means (such as cultured mammalian cells) and more risky because of transference of human pathogens. For a listing of relevant web resources and reports on plant-made pharmaceuticals, see Daughton/EPA (2002b). While these current-generation phytopharmaceuticals are proteins (and therefore at least have an innate susceptibility for degradation in the environment), questions must be asked as to the wisdom of mass-biosynthesis of pharmaceuticals in food-plants, whether the large quantities that can be produced will have the ability for direct escape to the environment (with the attendant unknowns of persistence and non-target, unanticipated effects), and whether the technology will eventually gain the routine ability to synthesize small-molecular non-proteins, which may pose different concerns than for proteins.

Contamination of the common agricultural food-plant gene pool by cross-pollination has been established as a major concern (albeit hotly debated), especially if the therapeutic were bioactive at trace concentrations (such as hormones). Cross-pollination is a major concern, as reflected by the current regulations on inter-crop distances and crop-cycle timing as stipulated in USDA (via the Animal & Plant Health Inspection Service, APHIS) and FDA regulations (see links at: Daughton/EPA 2002b). Furthermore, the crops most frequently used for molecular farming are corn, soybeans, and rice. Any progress in eliminating (as opposed to minimizing) the possibility of cross-pollination would be desirable — a true, closed-loop system would be preferable, as any controversy regarding contamination of the common food supply would then be negated. While the primary concern regarding risk has focused on humans (centered around allergenicity, and toxicity in the form of direct endocrine disruption or other mechanisms), perhaps more imminent (but largely unanticipated) hazards could be present for non-target organisms, whose interactions with crops are extremely difficult to prevent. Any failure of the systems in place to ensure the complete containment of plant-made pharmaceuticals could at the least lead to widespread distrust (and disruption) of the long-established and trusted U.S. food industry. Such concerns would at the least impact mass psychology. As an example, while a low level of contamination of non-genetically modified foodstuffs with herbicide-tolerant or insecticidal grain may be tolerable to some people, would the same level of tolerance continue if a drug for rheumatoid arthritis or a vaccine for hepatitis B were the contaminant? For in-depth discussions of the many complex facets of this topic, see: CFIA 2001; Freese 2002; Golz 2001; Kirk 2001; McCalla et al. 2002; Pew 2002; and other resources at Daughton/EPA (2002b).

Omics: As pointed out by Daughton and Ternes (1999), rapid and escalating advancements in genomics, proteomics, glycomics, and others, coupled with an inverting societal age structure will contribute greatly to the commercial introduction of an ever-increasing array of new drug entities, many of which target new receptors and possess previously unforeseen mechanisms of action. As an example, novel (non-native, "mutated" proteins) can now be theoretically engineered (using native biochemical machinery) by modification of existing proteins and incorporation of non-natural amino acids (e.g., see: Bessho et al. 2002). These "mutated" proteins may not be as easily catabolized as native proteins and therefore may have the potential for longer ecological half-lives. This fact, in light of the Precautionary Principle, provides ample forewarning to institute measures for minimizing the risks that might be associated with introducing drugs to the environment – and at the same time improve consumer health and economy.

Personal "Medical Statistics Card": A voluntary, personal "medical statistics card" containing an individual's medical treatment history could greatly assist in minimizing the overuse and inappropriate use of prescription drugs. The history stored on such a card (including past and present medication, allergies, etc.) could greatly assist an attending physician in avoiding redundant or ill-advised prescribing because of a lack of patient data; this would be especially valuable for those patients having multiple physicians and those who "self-medicate". It could even be used to help consumers in pre-screening OTC drugs and food supplements that could lead to adverse interactions with prescription medication they are taking. The consumer would not need to understand the status of any of the medications and supplements they are taking as long as they were diligent in using their card when purchasing medications or supplements; the card would rely on accessing a standardized, up-to-date expert system of prescribing information. Such a card, whose information content could be stored anonymously (no need to encode with personal information) would not be confused with the concept long and hotly debated in the U.S. of a "National Health Card," which is intended more for the purpose of obtaining medical services rather than ensuring efficiency and efficacy of medical treatment; National Health Cards have been successfully implemented for some time in a number of other countries, but have been controversial in the U.S. because of real or perceived issues with privacy protection. The patient could, however, also elect to store medical information keyed to their personal identity if they wished to avoid repeated requests for the same information by multiple medical care provides (and thereby also ensure a more accurate, thorough, and consistent portrayal of their medical histories across a continuum of providers).

INSIGHTS AND RECOMMENDATIONS: DISPOSAL of PPCPs by the ENDUSER

In North America, only a fragmented patchwork of often-contradictory regulations, guidance, and formal/informal advice attempts to direct the purposeful disposal of PPCPs. This uncoordinated guidance is geographically uneven, and varies greatly among governing bodies. Regardless of what the best environmental disposition of expired/unwanted PPCPs might eventually prove to be, clearly there would be benefits in having but one optimal approach. Much work is needed in formulating a single, cohesive set of nationwide (or global) regulations or guidance addressing disposal or recycling. Comprehensive regulations or guidance would address PPCPs that have entered the consumer chain, as well as those used in (i) hospitals, (ii) medical practices (such as physician's samples), (iii) long-term care facilities (such as nursing homes), and (iv) humanitarian relief efforts.

[Note to the reader: Locating literature regarding drug disposal is not easy, primarily because there are no unique search words. To broaden success in keyword searching of English documents available on the Internet and published in the printed literature, multiple terms must be used, including the coupling of the words "drug," "medicine" (or the adjective "medication"), or "pharmaceutical" with "disposal," "destruction," "recycling," "re-use," "return," "take-back," "outdated," or "expired." Once formal disposal/recycling program names have been identified (e.g., see EnviRx or RUM; see below: "Take-Back Programs"), they can be used in turn to locate many more references (this is especially useful for non-English Web pages).]

Current Practice – Patchwork of Diametrically Opposed Approaches: To illustrate the disharmony of current practices, consider the following. Most existing laws directed at drug disposal are written around two concerns: (1) the disposition of "controlled" substances or (2) the imperative to keep expired/unwanted medication away from children (this is perhaps the major imperative for disposing of drugs to sewage that has been instilled with the public over the years). Environmental concerns are rarely cited (in the U.S., California is one exception). Some states require nursing homes to dispose of unwanted drugs to the "toilet." For example, North Carolina (2002) regulations stipulate "Non-controlled substances shall be disposed of by incineration, flushing into septic or sewer system, or by transfer to a local pharmacy for destruction." Many pharmacy or health care Web sites recommend disposal to the sewer. Typical examples include: "Flush old drugs down the toilet; don't just toss them in the trash where little hands could get hold of them" (MSN 2002), and the California Poison Control System (2002), which advocates flushing unwanted drugs down the "toilet". Sometimes, the advice is nebulous and circular: "Contact your state board of pharmacy or your state Environmental Protection Agency office for the appropriate means of disposal of prescription samples. Local law enforcement may not be aware of specific disposal issues relating to prescription drugs" (Volunteers in Health Care 2001). In contrast, there are other Web sites that give more proactive advice. For example, Great Pacific Industries' (2002; e.g., Save-On-Foods) pharmacy network has its own "take-back" program (Bright Ideas for Environment "Medication Disposal Program"), more in line with a nationwide program that has been implemented in Canada since the mid-1990s and in Australia since 1998 (see next section: "Take-Back Programs").

Take-Back Programs: Most British Columbia pharmacies belong to the "Medications Return Program" (MRP). The MRP was instituted in March 2001 as a relaunch of the formerly known "EnviRx" program, which was founded in November 1996 as a consumer-oriented stewardship program, established voluntarily by British Columbia's pharmaceutical industry. The program's most recent annual report can be found here (Driedger 2002). The program was made mandatory in March 1997 by an expansion of the scope of the "Post-Consumer Residual Stewardship Program Regulation" (Government of British Columbia 2002). It is designed to accept the free return of all prescription and over-the-counter (OTC) medications (and certain other medically oriented products); it does not, however, accept physician samples. The MRP derives from a true cradle-to-cradle philosophy in that "ecology of health" is the central focus (see discussion in Part I, "Health of Ecology Versus Ecology of Health," Daughton 2003a). The MRP was formed to balance the concerns and objectives for ensuring or improving the health of the environment, consumer, and economy.

The MRP has been embraced by Canada's National Association of Pharmacy Regulatory Authorities (NAPRA) for a number of reasons, including consumer/child safety (accidental poisonings, unwitting consumption of expired product or product prescribed for someone else), reduced costs (encouraging purchase of manageable drug amounts that are fully consumed), improved therapeutic outcomes, and "reduced potential for environmental damage" (NAPRA 2002).

The Canadian take-back programs (as founded under EnviRx) have also had unforeseen benefits, especially for consumer health; such collateral benefits are characteristic of cradle-to-cradle approaches. For example, the Alberta Pharmaceutical Association (APhA) has been mining the data compiled from their program to answer questions regarding what consumer sectors are discarding PPCPs and why they are not fully using their supplies (Driver 1998). For example, a major problem long faced by medical practitioners has been "patient non-compliance" (why patients do not finish their medication). The Alberta take-back program provided the rare opportunity to perform a follow-up, life-cycle analysis — the type of study normally missing from current prescribing practices. The knowledge gained could prove extremely beneficial to the healthcare consumer. At the same time, potential adverse environmental impacts are reduced. The study learned, for example, that geriatric patients return the most medications. This led to the recommendation for "trial prescriptions" that provide small initial quantities, enabling the physician to determine the suitability of the prescription for the patient before large quantities go unused.

There are also some take-back programs in Europe. Two major ones are Italy's "Ass.Inde" and France's "Cyclamed" (e.g., see: Macarthur 2000). EMEA (2001, section 5: "Precautionary and Safety Measures...") also recommends that "unused preparations or old preparations should be returned to pharmacies." In Australia, a free "returns" program was launched in July 1998 using a not-for-profit organization (The National Return and Disposal of Unwanted Medicines Ltd.) in partnership with the NSW Government and various pharmaceutical industry entities. Dubbed the RUM Project (Return Unwanted Medicines), the program plans to enlist over 5,000 pharmacies nationwide. As with other take-back programs, RUM's mission is to lessen disposal to the environment, reduce child poisonings, and minimize inappropriate sharing of medicines (RUM 2002).

Sparse Literature: Surprisingly, the various facets of the topic of drug disposal have been infrequently addressed in the literature over the years, and the few papers that have been published in the open literature have received little attention outside the pharmacy community. The topic of drug disposal has interested medical professions primarily because of insights it can yield on issues relating to patient compliance and economic costs to the consumer. The driving force has rarely emanated from the potential for environmental benefits (which albeit are currently ill-defined because of a lack of science), although progress toward one aim is often relevant to the other – they are intimately tied. The two major issues are misuse and inappropriate use (both resulting in overuse) and non-compliance (resulting in discharge of unused drugs to sewage and solid waste when a course of medication is not completed). Inappropriate use especially among the elderly has been a topic of continuing debate (e.g., see: Gurwitz and Rochon 2002; Pitkala et al. 2002). The public needs to be better informed regarding the appropriate use of medications to maximize the benefits for themselves and the environment. The following is a synopsis of some of these relevant studies.

Coambs et al. (1997) reported that for Canada's health care system, the economic annual costs that could be potentially avoided by better engineering of prescribing practices and patient education (i.e., inappropriate use and medication noncompliance) were estimated to be as high as \$7-9 billion Canadian. More recent studies (e.g., CSHP 2002) corroborate the economic aspects: "Misuse of drugs is not only a major health concern, it is a major economic concern." In one of the earliest analyses of the economic costs of drug disposal, Kidder (1987) determined that monthly per-patient drug wastage costs ranged from \$1.52 to \$5.67.

Boivin (1997) reports some of the only actual survey data on drug disposal. As many have noted, as the population age structure becomes more inverted, the number of prescriptions per patient also tends to increase; for example, in 2000 those patients age 75 and older received per capita the most new prescriptions — an average of 12 (NACDS 2002). But not only does medication use rise with age, it also tends to result in more wastage (for a variety of reasons, most of which result from issues specific to geriatric medicine). Boivin discovered that substantial quantities of drugs go unused from both classes of therapeutics — acute (short term) and maintenance (long-term). Many of the most frequently unused (returned) drugs also happened to be ones that have since been identified in environmental monitoring studies (e.g., see: Daughton and Ternes 1999). Factors found to contribute to non-compliance include: frequent physician alterations in dosage of existing drugs and prescribing of new drugs, patient death, patient improvement, and silent symptoms (those that the patient cannot detect as worsening or improving, such as high blood pressure, and which provide the patient with no feedback or incentive for continuing with their medication). The survey indicated that more than 63% of the population had disposed of medication in the past. The estimated annual cost of the wasted medication across the province of Ontario exceeded $40,000,000; if extended for all of Canada, the wastage could have exceeded $110,000,000. With regard to the method of disposal (prior to the Canadian take-back program), 46% had disposed of their unwanted medications to the toilet, 31% disposed them to trash, 17% had already been taking them back to the pharmacy, 2% to their physician, and 4% used other routes. The predominance of disposal to the toilet over other routes, corroborates the few other published studies, despite claims to the contrary (e.g., see Velagaleti et al. 2002).

In a study of drug use at LTCFs, Paone et al. (1996) make a number of recommendations regarding the reduction of medication usage. They found medication wastage to amount to 6.7% of the total cost of dispensed medications. This resulted in part from problematic "prn" (take as needed) medication and because medication was discontinued by physicians 27% of the time because it was no longer needed or suitable, whereas the dose of medication was altered in 5% of patients. They recommended that dispensing be limited to 10-day (instead of 30-day) supplies.

The American Medical Association's Council on Scientific Affairs addresses the issue of drug "recycling" (AMA 2001) and reaches the conclusion that the costs associated with LTCF unused medications is between 4 and 10% of the total dispensed costs. Of the wastage, more than 90% results from "discontinuation or change in medication or death, transfer, or hospitalization of the resident." But they were not able to assess the method by which this substantial quantity of unreturned medication was disposed. The AMA encourages the use of tamper-evident seals on medication to facilitate return/recycling. The AMA policy is consistent with the policy of the American Society of Consultant Pharmacists (ASCP 1996), which "supports the return and reuse of medications to the dispensing pharmacy to reduce the waste associated with unused medications in long-term care facilities and to offer substantial cost savings to the health care system...".

Very sparse data are available that indicate the quantities of drugs that are purposefully disposed. The Australian RUM Project (RUM 2002) has recently been collecting over 200 tons of unwanted drugs each year; this perhaps gives a glimpse as to the magnitude of the disposal issue. In one of the only published surveys relevant to the U.S., Kuspis and Krenzelok (1996) also surveyed community drug disposal. Of those surveyed, only 1.4% returned medications to a pharmacy, 54% disposed of medications in the garbage, and 35.4% flushed medications down the toilet or sink; 7.2% did not dispose of medications, and 2% said that they used all medications before expiration. Of the pharmacies surveyed, 97% had specific policies regarding disposal of undispensed medications, and these policies directed return to the producer. For medication that was not returnable, 15% was incinerated, 17% directed to hazardous waste handlers, and 68% disposed to solid waste or the toilet (but unfortunately, the two were not distinguished). In contrast to internal operating procedures, only 5% of the surveyed pharmacies had consistent recommendations for their customers. Little information on safe disposal of drugs was routinely relayed to the public. The authors recommend that uniform guidelines are needed for the safe disposal of expired medications and these policies should be included in consumer education provided by pharmacies and poison information centers alike. Indeed, note that the California Poison Control System (2002) advocates flushing unwanted drugs down the "toilet". For the 12-month period prior to the COMPAS survey (for Health Canada), 19% and 20% of those surveyed disposed of unused/expired non-prescription and prescription drugs, respectively, to sewage (with higher percentages of woman doing so than men), and 50% and 39% disposed of non-prescription and prescription drugs to the garbage, respectively (COMPAS 2002); interestingly, 26% and 37% disposed of these by a means other than garbage, recycling, sewage, or dumping/burying.

Only as recently as the late 1990's was the concept of "treating the environment as our patient" (in line with the "ecology of health"; see Part I, "Health of Ecology Versus Ecology of Health," Daughton 2003a) beginning to emerge from the pharmacy sector (e.g., see: Blanchard 1998). Blanchard noted a survey recommendation that reducing a prescription's supply to 28 days could reduce the need for discarding by as much as 30% (but also noted that progress in that direction is hampered by the desires of insurers and patients, both of whom want bulk filling of prescriptions). Blanchard also noted, that with the issue of waste aside, 28-day supplies would also reduce inappropriate use of leftover medications and accidental poisonings.

DISPOSAL GUIDANCE

Little formal guidance has been developed for drug disposal. The World Health Organization (WHO) was forced to develop guidance as a result of the humanitarian efforts during the Bosnia conflict. A major problem arose from the enormous quantities of expired and inappropriate medications that were received as part of humanitarian donations. But the WHO's guidance (1999) is more relevant to large-scale field situations.

The Canadian "National Association of Pharmacy Regulatory Authorities" (NAPRA) has also taken a proactive stance toward drug disposal (e.g., see: NAPRA 2002); their philosophy is reflected in the consumer pamphlet prepared by CPhA (2002), which gives the consumer tips on disposal of unwanted drugs, including guidance to not dispose drugs in the garbage or to the toilet — because "it's not good for the environment".

The American Pharmaceutical Association (APhA) coordinated the development of the 1998 Pharmacist Practice Activity Classification (PPAC) system (APhA 1998), which describes and classifies the activities of licensed pharmacists throughout the health care delivery system. Activity C.3.4. in the PPAC ("Promote safe medication use, storage and disposal") has two tasks involving drug disposal: Task C.3.4.4 ("Educate groups about the proper disposal of medications and devices") and Task C.3.4.5 ("Provide a general medication and device disposal service pursuant to state and federal laws and regulations"). But specifics are not provided on their web site.

For the most part, however, a large disjointed patchwork of often conflicting guidance and regulations exist for directing the disposal or destruction of drugs. It has long been common knowledge amongst pharmacists and physicians, at least in some states and locales that oversight/regulatory authorities do recommend "proper disposal" of drugs but at the same time, they contradictorily recommend disposal to sewage. Oversight regarding disposal/destruction usually resides in a variety of agencies and departments, and those that oversee pharmacies differ from those that oversee nursing facilities, and others yet sometimes oversee consumer end-use (Light 1997).

The importance of uniform guidance for disposal of PPCPs is illustrated by one of the outcomes from the American Academy of Pediatrics (AAP) policy statement on the implications of mercury in pediatric health care (Goldman et al. 2001). One of the many sources for mercury in the environment is from personal care products and devices such as mercury thermometers. One of the recommendations set forth to pediatricians by the AAP policy statement was for "parents to remove mercury thermometers from their homes." Unfortunately, advice on the proper methods for disposal of elemental-mercury thermometers did not accompany the report. A follow-up study (DiCarlo et al. 2002) surveyed a variety of local, county, and state health officials to ascertain the advice that they would be giving to public inquirers regarding proper thermometer disposal. The percentage that would have made the correct recommendation (namely, turn thermometers in to hazardous waste pickup) was only 24%. The major (and incorrect) recommendation would have been to dispose in domestic trash (45%). This one example (that should have been clear cut) shows the importance of unified, clear guidance regarding disposal or recycling of all medical products.

HAZARDOUS CHEMICALS - a SPECIAL and PARADOXICAL CASE regarding PPCPs

There does exist a special circumstance where the disposal of specific drugs and ingredients in personal care products is indeed regulated – namely, chemicals listed as hazardous under RCRA (Resource Conservation and Recovery Act). The U.S. Department of Justice, Drug Enforcement Agency strictly regulates the disposal of unwanted controlled substances (but there are many exemptions, depending on factors such as whether the substance is used in a prescription medication, e.g., pentobarbital, phenobarbital, diazepam, codeine, and many others). The DEA disposal program is not discussed here. The "Schedules of Controlled Substances" can be obtained from CFR (2002a). The DEA classifies controlled substances into five categories (Schedule I through Schedule V), indicating progressively lower potential for substance abuse. Schedule I substances have a high potential for abuse (and no recognized medical uses); the other schedules contain drugs with recognized medicinal uses.

For a drug to be RCRA listed, it generally must appear on the "P" or "U" lists. P-List RCRA chemicals are deemed acutely hazardous in any concentration (40 CFR 261.33e); U-list chemicals are deemed less toxic (40 CFR 261.33f). Quite a number of PPCPs appear on these lists primarily because of toxicity (indicated as "T"); the other hazardous properties are "R" (Reactivity), "I" (Ignitability), and "C" (Corrosivity). Some RCRA-listed chemicals that have major medicinal therapeutic uses are listed in Table 1 (but note that many other non-medicinal chemicals on these lists are commonly used in various other aspects of medicine and therapeutics). For the complete lists, refer to 40CFR§261.33 (CFR 2002b). Whether a PPCP is available only by prescription is not a determining factor for listing. Some listed PPCP ingredients are "over-the-counter" (OTC) constituents (e.g., nicotine). These issues are further discussed by Smith (1999, 2002).

These and other commonly used PPCP ingredients become hazardous waste at the time the decision is made to actually dispose. The responsibility for determining if the waste is indeed hazardous rests with the waste generator. As mentioned above, note that for the controlled substances (such as codeine, opiates, tranquilizers, etc.), DEA regulations apply. While RCRA directs the disposition of certain select PPCPs, this determines how distributors and pharmacies handle these drugs when they are out-dated. The significant point in the present discussion follows. The law is not closed around the complete use-cycle, as it has no impact on the actions of consumers. For example, mention is never made on a drug container that the ingredients are subject to RCRA. But even then, the fact that a drug is RCRA-listed and handled appropriately still does not prevent it from entering the environment – because the mere use of these substances by consumers results in direct input to the environment – by both excretion (currently unavoidable) and consumer disposal.

A paradox arises in that many regulated industrial chemicals have dual uses – as consumer non-food products and as industrial chemicals. They are not subject to the same strict disposal standards for consumer use as they are for industrial use. Phthalic acid esters (phthalates) are but one example; others include a wide array of common solvents, including alkanes, alcohols, aldehydes, ketones, esters, and aromatics (all of which can be used in formulating cosmetics). The consequence is that substantial exposures to very high concentrations of regulated substances can result from direct application to the body by unregulated use.

The CDC published the first large scale environmental contaminant human exposure study through direct biomonitoring of blood and urine (Blount et al 2000; CDC 2000b). The study verified human exposure to chemicals via personal care products — namely phthalates. These ubiquitous, high-volume industrial chemicals (often used as flexibility-promoters in plastics) have a plethora of end uses in consumer products, including vinyl flooring, wall coverings, detergents, lubricating oils, solvents, food packaging, and medical devices. They also are frequently used in many formulations of PPCPs — for example, soap, shampoo, hair spray, sunscreens, antiperspirants, medication, and many types of nail polish; their uses are designed around the very abilities of phthalates to penetrate the skin and to act as humectants and emollients. They are incorporated into formulations at high concentrations. Their use has been so widespread for such a long time, that they are frequent background contaminants in environmental analyses. The CDC study showed that human exposure is higher and spans a wider spectrum of phthalates than previously suspected. Exposure of wildlife is unknown, but given the widespread and heavy use of these compounds, exposures to a wide array of organisms can be inferred.

CONCLUSIONS/RECOMMENDATIONS

A patchwork of inconsistent, and often conflicting advice, guidance, or regulations exist among and within countries to guide the disposal of PPCPs and ultimately determine their environmental disposition.

Despite this patchwork, a wide array of actions could be taken both near-term and longer-term to lessen the introduction of PPCPs to the environment. Given the state of current information regarding the occurrence of PPCPs in the environment, disposal of drugs to domestic sewage systems is probably the LEAST desirable way to dispose of any drug. In the U.S., two better alternatives might include reworking existing regulations that prevent (1) local pharmacies from taking back consumer medications (to either dispose of by medical incineration or return to "reverse distributors"), or (2) local hazardous waste collectors from collecting unwanted medications (e.g., community curb-side pickup programs, but not for RCRA- or DEA-listed PPCPs). As a last alternative, disposal in household trash destined for engineered landfills is probably more environmentally sound (but still not desirable) than disposal to sewage systems; landfills, however, are really a form of potential "pollution postponement" — as opposed to an ultimate solution. Coincidentally, efforts to reduce the introduction of PPCPs to the environment often could and can have unforeseen, collateral benefits for consumer health and economies. Protecting the health, safety, and pocketbook of the patient holds potential for protecting the environment – and vice-versa. Such wide-ranging benefits are characteristic of cradle-to-cradle stewardship programs. Stewardship programs (centered around a cohesive take-back or returns program) would prove critical to the birth of the "green pharmacy." For true cradle-to-cradle stewardship of PPCPs, a holistic, integration of all aspects of the production-consumption cycle is required — one that takes into consideration the needs and costs of the complete cycle from drug discovery/design to distribution, end-use, and disposal/recycling. The economies and ecological/human health efficiencies of no single aspect can be optimized in isolation from the others. While the discussion in this paper surveys many of the avenues for reducing the controllable introduction of PPCPs to the environment, it does not address the many other issues (especially the potential for adverse effects) associated with the unintended, uncontrollable excretion of PPCPs and their metabolites into the environment – a subject of a future publication.

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Table 1. Some RCRA-listed chemicals that have major medicinal therapeutic uses

Representative P-listed drugs (some have other uses)	The U-list has a number of antineoplastic agents (among other PPCPs)
Epinephrine (adrenaline) P042	Chlorambucil (Leukeran) U035
Nicotine P075	Cyclophosphamide (Cytoxan, Neosar, Procytox) U058
Nitroglycerine P081	Daunomycin (Dauorubicin; Cerubidine) U059
Physostigmine P204	Diethylstilbestrol U089
Physostigmine salicylate P188	Melphalan (Alkeran)U150
Warfarin >.3% P001	Mitomycin C (Mutamycin) U010
	Paraldehyde U182
	Phenacetin U187
	Reserpine U200
	Saccharin U202
	Selenium sulfide U205 (e.g., dandruff shampoos)
	Streptozocin (Zanosar) U206
	Uracil mustard U237
	Warfarin (Coumadin) <.3% U248